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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/590,992	09/27/2006	Torsten Dunkern	27577U	4187

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EXAMINER	
SZNAIDMAN, MARCOS L	
ART UNIT	PAPER NUMBER
1611	

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06/17/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/590,992	DUNKERN ET AL.	
	Examiner	Art Unit	
	MARCOS SZNAIDMAN	1611	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 January 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-28* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-28* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6 pages / 11/14/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to applicant's reply filed on January 7, 2008.

Election/Restrictions

Applicant's election with traverse of: Sidenafil as the PDE5 inhibitor and Sepsis associated encephalopathy, as the indication in the reply filed on January 7, 2008, is acknowledged. The traversal is on the ground(s) that all the chemical species are PDE5 inhibitors, so there is unity of invention. This is not found persuasive because the PDE5 inhibitors in claim 23 have a very diverse set of compounds that do not belong to a single core structure, for example Sildenafil (Viagra) has piperazine sulfonamide that is not present in Tadalafil (Cialis), while Tadalafil has an indole structure that is not present in Sildenafil. Regarding the disorders grouped under "impairment or dysfunction of cerebral vascular reactivity" listed in claim 21 like: sepsis and autoimmune thyroditis, will require a different patient population and different methods of treatment. Each one has a different pathology, for example: sepsis is broadly defined as the presence of various pus-forming and other pathogenic organisms, or their toxins, in blood or tissues that causes a whole body inflammation. On the other hand, thyroiditis is the inflammation of the thyroid gland, which is normally caused by either infection, like a virus or bacteria, or by a malfunction of the immune system.

The requirement is still deemed proper and is therefore made FINAL.

Status of Claims

Claims 21-28 are currently pending and are the subject of this office action.

Claims 21-28 are presently under examination.

Priority

The present application is a 371 of PCT/EP05/250958 filed on 03/03/2005, and claims priority to EPO 04100909.3 filed on 03/05/2004.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 21-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is an enablement rejection.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fd. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect

to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996). As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1- the quantity of experimentation necessary,

2- the amount of direction or guidance provided,

3- the presence or absence of working examples,

4- the nature of the invention,

5- the state of the prior art,

6- the relative skill of those in the art,

7- the predictability of the art, and

8- the breadth of the claims

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. <u>The nature of the invention</u>

Claims 21-28 recite a method of treating sepsis associated encephalopathy (SAE, species elected) with a therapeutically effective amount of Sidenafil (species elected).

2. The state and predictability of the art

At this moment, a specific treatment for SAE does not exist and outcome relies upon prompt and appropriate treatment of sepsis as a whole (Green et. al., Front. Biosci. (2004) 9:1637-1641, mentioned by applicant, see specification end of page 8 and beginning of page 9). Wratten (European Journal of Anaesthesiology (2008) 25 (Suppl. 42): 1-7) mentions that septic animal models are often limited to young healthy animals with no existing comorbidities. They often use well-defined exaggerated doses of endotoxin or bacterial infiltrates and usually do not mimic the various clinical conditions (such as the presence of hyperdynamic and hypodynamic shock, ventilatory support, use of antibiotics and other drugs). (see page 3, second paragraph).

In other words, there is no treatment for SAE and there are no good animal models to predict efficacy of treatments in humans.

3. The relative skill of those in the art

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. The artisan using Applicant's invention would generally be a physician with a M.D. degree and several years of experience.

4. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides animal data for the treatment of SAE with Sidenafil in rats (see example 3 on page 12). The example does not mention haw many animals were treated with this method, nor does it mention the amount of Sidenafil required to achieve these results, and there is no dose response curve to asses the efficacy of Sidenafil in this model. Results are based on the measurement of two parameters: somatosensoric evoked neuronal potential (SEP) and evoked cerebral flow.

5. The quantity of experimentation necessary

In the absence of reliable animal models in the prior art (see above discussion) and in the absence of experimental evidence commensurate with the scope of the claims, the skilled artisan would not accept that Sidenafil could be predictably used as treatment for SAE. Since there is no precedent in the literature for the treatment of SAE with Sidenafil or any other PDE5 inhibitor, how is the skilled physician supposed to know how to dose Sidenafil, or any other PDE5 inhibitor in order to treat SAE? Determining if Sidenafil would treat SAE, would require formulation into a dosage form, and subjecting into clinical trials or to testing in an assay known to correlate to clinical efficacy of such treatment. This is undue experimentation given the limited guidance and direction provided by Applicants.

Accordingly, the inventions of claims 21-28 do not comply with the scope of enablement requirement of 35 U.S.C 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation with no assurance of success.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCOS SZNAIDMAN whose telephone number is (571)270-3498. The examiner can normally be reached on Monday through Thursday 8 AM to 6 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael P. Woodward can be reached on 571 272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/MARCOS SZNAIDMAN/
Examiner, Art Unit 1611
April 30, 2008

/MP WOODWARD/
Supervisory Patent Examiner, Art Unit 1615